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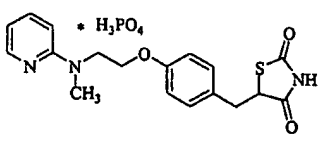
(54) Title: SALT OF PHOSPHORIC ACID WITH 5-[4-[2-(N-METHYL-N-(2-PYRIDYL)AMINO)-ETHOXY] BENZY] THIAZOLIDIN-2,4-DIONE AND A METHOD OF ITS PREPARATION



(III)

(57)-Abstract: The salt of phosphoric acid with 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidin-2,4-dione of formula III including its tautomers and solvates. Formula (III).

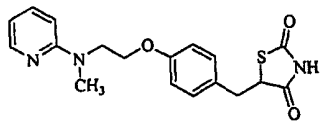
SALT OF PHOSPHORIC ACID WITH 5-[4-[2-(N-METHYL-N-(2-PYRIDYL)-AMINO)ETHOXY]BENZYL]THIAZOLIDIN-2,4-DIONE AND A METHOD OF ITS PREPARATION

Technical Field

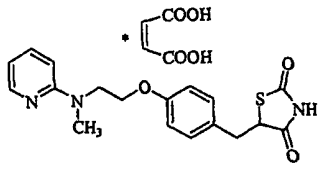
The invention concerns a new salt of rosiglitazone, i.e. of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)-ethoxy]benzyl]thiazolidin-2,4-dione, with phosphoric acid (H_3PO_4), including a method of its preparation and physical and chemical properties. The salt can be used to prepare pharmaceuticals for treatment of hyperglycemia in patients with *diabetes mellitus* of type 2.

Background Art

Rosiglitazone, chemically 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidin-2,4-dione of formula I, is a known anti-hyperglycemic agent, which was first described in patent EP306228 (1989) of Beecham. Rosiglitazone is in praxis used in the form of salts, especially with maleic acid (WO 9405659 A1, formula II). Recently, a number of crystalline modifications of rosiglitazone maleate II and of its hydrates have been known (WO 2000064893 A2 and WO 2000064892 A2, WO 2002026737 A1, WO 9931095 A1, WO 9931094 A1 and WO 9931093 A1). A number of other addition salts is also known, both with mineral acids and with strong organic acids (WO 0220519 A1, WO 0220518 A1).



I



II

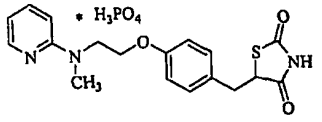
The solution being described comprises a new salt of rosiglitazone of formula I with phosphoric acid, which surprisingly shows a number of advantageous qualities that have not yet been observed in the above described salts.

Disclosure of Invention

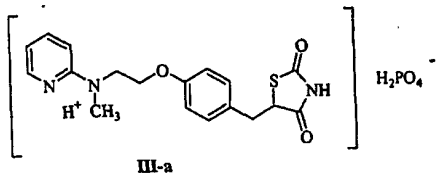
The invention concerns a salt of phosphoric acid with 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]-benzyl]thiazolidin-2,4-dione, described by formula III, and a method of its preparation. The method allows preparing a hitherto undisclosed salt of rosiglitazone of

formula I with phosphoric acid (H_3PO_4) in high yield and quality required for pharmaceutical substances.

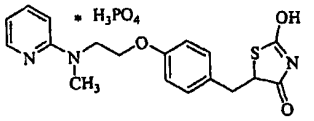
From the chemical point of view, our product is a salt that contains a component described by formula I and phosphoric acid (H_3PO_4) in the ratio 1:1, i.e. rosiglitazone dihydrogenphosphate. The chemical structure of the salt we have obtained can be described by formulae III, III-a, III-b and III-c, which are equivalent to each other. However, for the sake of simplicity, formula III will be used further on in the text. It can be assumed that the obtained salt shows anti-hyperglycemic activity as do other salts of rosiglitazone. An economically viable method of preparation of the salt has also been found, which can be used also on the production scale.



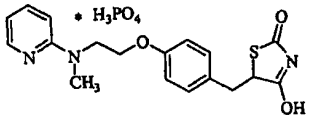
III



III-a

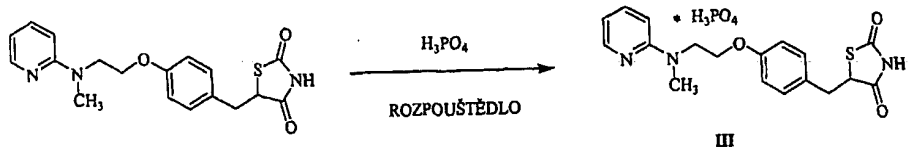


III-b



III-c

The method of preparation according to the invention consists in a reaction of 5-[4-[2-(N-methyl-N-(2-pyridyl)-amino)ethoxy]benzyl]thiazolidin-2,4-dione of formula I with concentrated phosphoric acid or its solution, which is carried out in an organic solvent. The manufacture of the salt of formula III can be preferably carried out at a temperature close to the boiling point of the used solvent, where good solubility of the starting compound of formula I is ensured. However, the reaction itself can take place at a wide range of temperatures, including temperatures higher than the boiling point of the used solvent at atmospheric pressure. In order to ensure successful accomplishment of the reaction, one can chose reaction temperatures from the interval of 0 up to 150 °C. The process of preparation of the salt of formula III is described by the equation in Scheme 1.

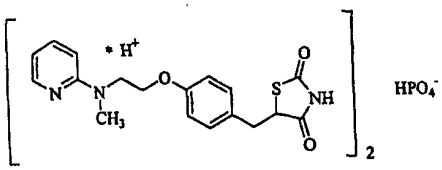


I III

Scheme 1

The choice of the solvent depends on solubility of the starting substance and the product. Alcohols (e.g. methanol, ethanol, 1-propanol, 2-propanol, butanols), esters of carboxylic acids (e.g. ethyl acetate), ethers (e.g. dioxane, tetrahydrofuran, diethyl ether), ketones (e.g. acetone, cyclohexanone), acetonitrile, their arbitrary mixtures and mixtures with water in any ratios can be used as solvents.

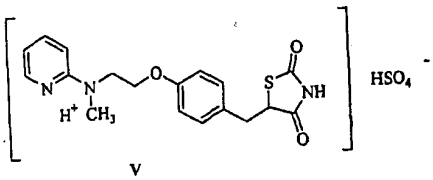
Surprisingly, for the compound according to the invention described by formula III no capability of reacting chemically with another fraction of free base of rosiglitazone has been observed. This is because it has been found out experimentally that a reaction of two equivalents of the free base of rosiglitazone of formula I with one equivalent of phosphoric acid (H_3PO_4) does not yield the expected salt, which is described by formula IV, but an equimolar mixture of the salt of formula IIII and the free base of rosiglitazone of formula I.



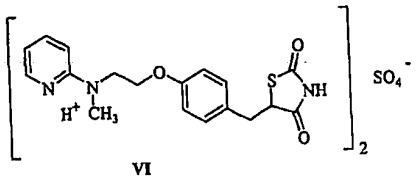
IV

The effect was not observed with any other salts of rosiglitazone with polybasic mineral acids and it has a tremendous impact on achievable purity and stability of the product.

For example, in reaction of the free base of rosiglitazone with sulfuric acid two types of salts can result depending on the molar ratios of the starting compounds (WO 2003050113 A1, WO 2003050114), which are described by formulae V and VI. Accordingly, imprecise batching of the starting components involves the risk of formation of mixtures of sulfates of both types. In the manufacture it is necessary to avoid formation of these secondary salts by careful control of the course of the process, optionally by re-crystallizing the product.



V



VI

Moreover, if an excess of phosphoric acid is used in reaction of the compound of formula I with phosphoric acid (Example 4), the reaction yields a crystalline salt of formula III as the exclusive product, which contains the compound described with formula I and phosphoric acid (H_3PO_4) in the ratio 1:1. There is, therefore, no possibility of contamination even with potential salts where several molecules of phosphoric acid would bind to rosiglitazone.

These facts directly imply that in case of rosiglitazone phosphate of formula III chemical purity of 99.5% and higher, with content of individual impurities bellow 0.1%, including other undesired phosphates, can be obtained without any problem.

An advantageous form of the salt of formula III is the crystalline form, which is chemically stable, chemically very pure (above 99.5% according to HPLC), well soluble in water and in aqueous solutions of hydrochloric acid, which can be prepared in high yields in the defined crystalline modification, and which is characterized by suitable particle size for further processing. The crystalline form of the salt of formula III, prepared by us, meets these requirements.

The crystalline structure of this salt of formula III has been uniquely characterized by the results of the following analytical methods: X-ray powder diffraction (XRPD), melting point, differential scanning calorimetry (DSC), ^{13}C and ^{31}P CP-MAS NMR and FT-IR spectroscopy. The results of analyses are presented in Examples and Appendices.

Contrary to some other salts of rosiglitazone, the above-described crystalline salt of formula III is well soluble in water and in aqueous solutions of hydrochloric acid. Especially the solubility in solutions of hydrochloric acid is very important considering the acidobasic conditions in the digestive system (especially in the stomach). It offers indication of the solubility of the substance after it is digested, which is a very important factor for evaluating pharmaceutical effectiveness of the substance. A comparison of the solubility of the salt of

formula III in acidic environment with that of several other rosiglitazone salts is documented in Example 7. For example, 1 g of the crystalline salt of formula III can be completely dissolved in 18 ml of 0.1 M aqueous solution of hydrochloric acid at 20 °C. However, neither the same amount of rosiglitazone hydrochloride prepared according to WO 2000/063205 nor the same amount of pharmaceutically used rosiglitazone maleate of formula II prepared according to WO 9405659 could be dissolved under the same conditions.

It is especially advantageous to prepare the crystalline form of the salt of formula III according to the invention if the solvent is ethanol or its mixture with water at any ratio. The reason is good reproducibility of the procedure both for the small and for the large batches (Examples 1 and 2), moreover the process yields exclusively a defined crystalline modification (DSC and XRPD) and defined particle size; in addition the process is characterized by high yields, which are being achieved reproducibly. The listed properties of the crystalline salt of formula III are very advantageous for its production and pharmaceutical use.

The described process produces repeatedly, with yields of 90 to 95%, a crystalline salt of phosphoric acid with 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidin-2,4-dione, described by formula III, which had in all the cases the same and uniquely defined crystalline modification, which is documented by the results of comparative XRPD measurements in Figure 1.

This procedure allows obtaining of a crystalline product with particle of 1 to 100 μm, more than 95 % of particles being characterized by their maximum dimension smaller than 50 μm. This result was obtained without using complicated grinding or other disintegration. The particle size is extraordinarily important for pharmaceutical use of the product and it is often very labor-intensive or impossible to obtain a product that would have suitable particle size. Methods of manufacture that produce such a product directly are, therefore, unique and exceptionally desirable.

The obtained salt of phosphoric acid with 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]-benzyl]thiazolidin-2,4-dione, which is described by formula III, can be used to prepare pharmaceutically applicable compositions, especially drugs with anti-hyperglycemic effect.

The subject matter of the invention is explained in more detail in the following examples, which, however, do not limit the extent of the invention defined in the claims in any respect.

Brief Description of Drawings

Fig. 1 is the X-Ray powder diffraction of the crystalline salt of phosphoric acid with rosiglitazone (III) prepared according to Examples 1 and 2.

Fig. 2 depicts the DSC curve of the crystalline salt of phosphoric acid with rosiglitazone (III) prepared according to Example 1.

Fig. 3 depicts the DSC curve of an equimolar mixture of the crystalline salt of phosphoric acid with rosiglitazone (III) and the free base of rosiglitazone (I) prepared according to Example 3.

Fig. 4 is the ^{13}C CP-MAS NMR spectrum of the crystalline salt of phosphoric acid with rosiglitazone (III) prepared according to Example 1.

Fig. 5 is the ^{31}P CP-MAS NMR spectra of the crystalline salt of phosphoric acid with rosiglitazone (III) prepared according to Example 1.

Fig. 6 is the FT-IR spectra of the crystalline salt of phosphoric acid with rosiglitazone (III) prepared according to Example 1.

Fig. 7 depicts a diagram of distribution of particle sizes according to the maximum dimension (MaxFeret) for the crystalline salt of phosphoric acid with rosiglitazone (III) prepared according to Example 1.

Examples

EXAMPLE 1

10 g of the free base of rosiglitazone **(I)** was dissolved in 250 ml of boiling ethanol. To the obtained solution, a solution of 1.8 ml of concentrated phosphoric acid (85% H_3PO_4) in 20 ml of ethanol was added. It was left to cool down freely under stirring for 2.5 hours. After filtration, washing of the filtration cake with 30 ml of ethanol and drying in a vacuum drier, crystalline salt **III** was obtained, m.p. 173-175 °C. The chemical purity of the product was 99.81 % according to HPLC. Contents of individual impurities were always lower than 0.1 %. The yield was 92 %.

EXAMPLE 2

40 g of the free base of rosiglitazone **(I)** was dissolved in 900 ml of boiling ethanol. To the obtained solution, a solution of 7.2 ml of concentrated phosphoric acid (85% H_3PO_4) in 100 ml of ethanol was added. It was left to cool down freely under stirring for 2 hours. After filtration, washing of the filtration cake with 100 ml of ethanol and drying in a vacuum drier, crystalline salt **III** was obtained, m.p. 174-175 °C. The yield was 91 %.

EXAMPLE 3

10 g of the free base of rosiglitazone **(I)** was dissolved in 250 ml of boiling ethanol. To the obtained solution, a solution of 0.9 ml of concentrated phosphoric acid (85% H_3PO_4) in 20 ml of ethanol was added. It was left to cool down freely under stirring for 2.5 hours. After filtration, washing of the filtration cake with 30 ml of ethanol and drying in a vacuum drier, a crystalline product was obtained, which was an equimolar mixture of salt **III** and rosiglitazone **I**. The DSC curve measured for the obtained mixture of I and III is shown in Figure 3.

EXAMPLE 4

10 g of the free base of rosiglitazone **(I)** was dissolved in 250 ml of boiling ethanol. To the obtained solution, a solution of 3.6 ml of concentrated phosphoric acid (85% H_3PO_4) in 40 ml of ethanol was added. It was left to cool down freely under stirring for 2.5 hours. After filtration, washing of the filtration cake with 30 ml of ethanol and drying in a vacuum drier, crystalline salt **III** was obtained, m.p. 173-175 °C. The yield was 93 %.

EXAMPLE 5

10 g of the free base of rosiglitazone **(I)** was dissolved in 250 ml of boiling acetonitrile. To the obtained solution, a solution of 1.8 ml of concentrated phosphoric acid (85% H_3PO_4) in 20 ml of acetonitrile was added. It was left to cool down freely under stirring. After filtration, washing of the filtration cake with 20 ml of acetonitrile and drying in a vacuum drier, crystalline salt **III** was obtained, m.p. 170-173 °C. The yield was 98 %.

EXAMPLE 6

10 g of the free base of rosiglitazone **(I)** was dissolved in 250 ml of boiling isopropylalcohol. To the obtained solution, a solution of 1.8 ml of concentrated phosphoric acid (85% H_3PO_4) in 20 ml of isopropylalcohol was added. It was left to cool down freely under stirring. After

filtration, washing of the filtration cake with 50 ml of isopropylalcohol and drying in a vacuum drier, crystalline salt **III** was obtained, m.p. 172-174 °C. The yield was 97 %.

EXAMPLE 7 – solubilities of rosiglitazone salts

Solubility was determined for crystalline rosiglitazone phosphate of chemical formula **III**, which was prepared by the procedure according to Example 1. 1 g of crystalline salt **III** was dissolved under stirring and at 20 °C without any residue in 18 ml of a 0.1M solution of hydrochloric acid within one minute. At the same conditions, neither dissolving of the same amount of rosiglitazone hydrochloride prepared by the procedure of WO 2000063205 nor of the same amount of pharmaceutically used rosiglitazone maleate **II** prepared according to WO 9405659 has succeeded. No solutions could be obtained even after extension of the time for dissolution was extended and another dilution with a 0.1 M solution of hydrochloric acid.

ANALYTICAL DATA (A-G): The following analytical data clearly characterize the crystalline salt of rosiglitazone phosphate of chemical formula **III**.

A X-Ray Powder Diffraction (XRPD)

XRPD diffraction patterns of crystalline salts of rosiglitazone phosphate **III**, which were prepared according to Examples 1 and 2 are shown in **Figure 1**. The values of characteristic diffraction angles are presented in Table 1. The diffraction patterns were measured using the diffractometer Seifert 3000 XRD at the following experimental conditions:

Radiation: CoKα (λ=1.7903Å)
Monochromator: graphite
Excitation potential: 35 kV
Anodic current: 35 mA
Measured range: 4 - 40° 2θ
Step size: 0.03 2θ
Sample: flat surface with thickness of 0.5 mm

Table 1

The values of characteristic diffraction angles 2θ and interplanar distances d of crystalline salt of rosiglitazone phosphate **III**

(° 2θ)	d (Å)	(° 2θ)	d (Å)
5.3	19.21	21.5	4.78
9.4	10.92	24.0	4.29
10.7	9.58	25.1	4.12
15.5	6.62	25.8	4.00
16.4	6.26	26.5	3.91
17.3	5.96	27.5	3.76
17.9	5.75	28.2	3.68
20.0	5.15	31.1	3.34
20.3	5.08	35.6	2.93
21.1	4.87	36.4	2.86

B Melting Point

The melting points of crystalline salts of rosiglitazone phosphate **III** were measured at Kofler's block with the heating rate of the sample of 10 °C (up to 150 °C) and 4 °C (above 150 °C) per minute. The measured values of melting points range from 170 to 178 °C. Typical melting-point values are presented in Examples 1-6.

C Differential Scanning Calorimetry (DSC)

The DSC recordings were measured using the instrument Perkin Elmer PYRIS 1. The measurements were performed for samples weighingt 3-5 mg. The samples were heated to temperatures 20-210 °C with the heating rate of 10 °C per minute. The measured DSC curves are presented in Figures 2 and 3. The crystalline salt of rosiglitazone phosphate **III** shows a maximum at the temperature 174 to 175 °C.

D Solid State Carbon NMR Spectra (^{13}C CP-MAS NMR)

The NMR spectra of the crystalline salt of rosiglitazone phosphate **III** for carbon isotope ^{13}C were measured using spectrometer Avance 500 Bruker with the measurement frequency

125.77 MHz using technique CP/MAS with sample rotation of 15 kHz. The obtained spectrum is presented in Figure 4. The locations of main peaks (chemical shift expressed in ppm) are: 175.3, 171.6, 156.6, 152.5, 147.0, 134.0, 129.7, 117.9, 113.1, 65.6, 54.9, 50.3, 40.6, 35.5.

E Solid State Phosphorus NMR Spectra (^{31}P CP-MAS NMR)

The NMR spectra of the crystalline salt of rosiglitazone phosphate **III** for phosphorus isotope ^{31}P were measured using spectrometer Avance 500 Bruker with the measurement frequency 202.46 MHz using technique CP/MAS with sample rotation of 15 kHz. The obtained spectrum is presented in Figure 5. The location of the peak (chemical shift expressed in ppm relative to the ammonium phosphate signal) is: 2.0.

F Fourier Transform Infrared Spectroscopy (FT-IR)

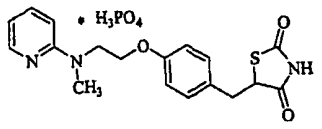
The infrared spectra of salt **III** were measured using the technique of KBr tablets at FT-IR spectrometer Perkin Elmer XB Spectrum with resolution of 8 cm^{-1}. The obtained spectra are presented in Figure 6. The locations of main peaks (wavenumber expressed in cm^{-1}) are: 2942, 2746, 1704, 1613, 1512, 1241, 1111, 956, 772.

G Measurement of Distribution of Particle Sizes

The distribution of particle sizes was measured microscopically with automatic evaluation of the measurement. A diagram of distribution of particle sizes according to the maximum dimension (MaxFeret) is presented in Figure 7. The measurement has shown that the crystalline salt of rosiglitazone phosphate **III** shows a distribution of particle sizes from 0 to 100 μm with the maximum in the interval of 0-10 μm (frequency of incidence about 68 %). More than 99 % of particles had its maximum dimension smaller than 50 μm.

CLAIMS

1. The salt of phosphoric acid with 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]-benzyl]thiazolidin-2,4-dione of formula III

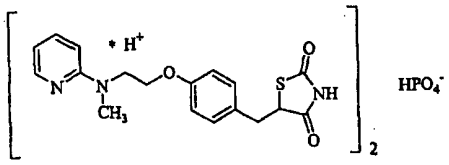


III

including its tautomers and solvates.

2. The salt according to claim 1, wherein the salt has a purity of 99.5 % (HPLC) and higher, with contents of individual impurities below 0.1 %.

3. The salt according to claim 2, wherein the salt contains less than 0.1 % of the phosphate of formula IV



IV

4. The salt of phosphoric acid with 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]-benzyl]thiazolidin-2,4-dione according to claim 1 in the crystalline form.

5. The salt according to claim 4, wherein the salt is characterized by the following reflections in the X-ray diffraction pattern: 5.3, 15.5, 21.5, 26.5, 35.6 (° 2θ).

6. The salt according to claim 4, wherein the salt is characterized by a melting point within the temperature interval of 170 to 178 °C.

7. The salt according to claim 4, wherein the salt is characterized by DSC with a maximum at 174 to 175 °C.

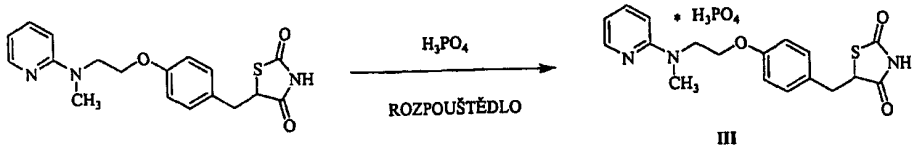
8. The salt according to claim 4, wherein the salt is characterized by the following FT-IR (KBr) bands: 1704, 1613, 1241, 1111 (cm^{-1}).

9. The salt according to claim 4, wherein the salt is characterized by the following signals in ^{13}C CP-MAS NMR: 175.3, 171.6, 156.6, 152.5, 147.0, 134.0, 129.7, 117.9, 113.1, 65.6, 54.9, 50.3, 40.6, 35.5 (ppm) and by the following signal in ^{31}P CP-MAS NMR: 2.0 (ppm).

10. The salt according to claims 1 through 9, wherein the salt is soluble in water and in aqueous solutions of hydrochloric acid.

11. The salt according to claim 10, wherein the salt is characterized in that 1 g of the salt of formula III dissolves in 10 to 20 ml of 0.1M hydrochloric acid within 1 to 10 minutes.

12. A method of preparation of the salt of phosphoric acid with 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidin-2,4-dione of formula III characterized in that 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]-thiazolidin-2,4-dione of formula I is reacted with concentrated phosphoric acid or with its solution, the reaction being carried out in an organic solvent.



I III

13. The method according to claim 12, characterized in that alcohols, esters of carboxylic acids, ethers, ketones, acetonitrile, their arbitrary mixtures and mixtures with water in any ratio are used as solvents.

14. The method according to claim 12, characterized in that ethanol or its mixture with water in any ratio is used as the solvent.

15. A crystalline salt obtainable according to claim 14, wherein said salt occurs as crystals having sizes from 1 to 100 μm, more than 95 % of the particles having their maximum dimension smaller than 50 μm.

16. Use of the salt according to claims 1 through 11 or 15 for the manufacture of pharmaceutically applicable compositions.

17. Use of the salt according to claims 1 through 11 or 15 for the manufacture of a medicament having anti-hyperglycemic effect.

Figure 1 X-Ray powder diffraction of crystalline salt of phosphoric acid with rosiglitazone (III) prepared according to EXAMPLES 1 and 2

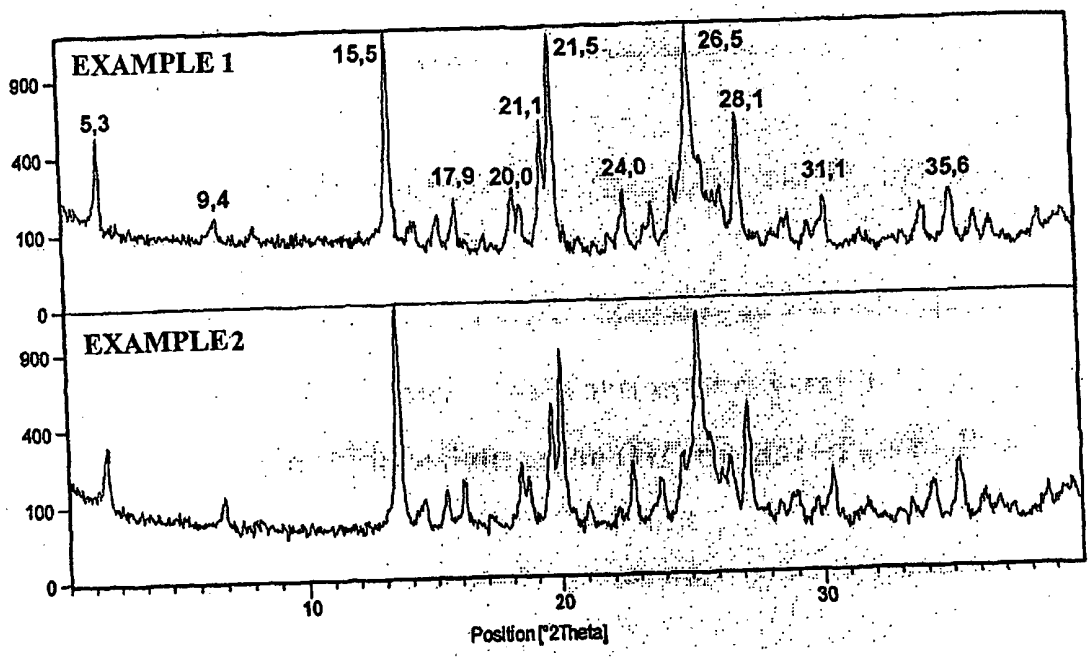


Figure 2 DSC curve of crystalline salt of phosphoric acid with rosiglitazone (III) prepared according to EXAMPLE 1

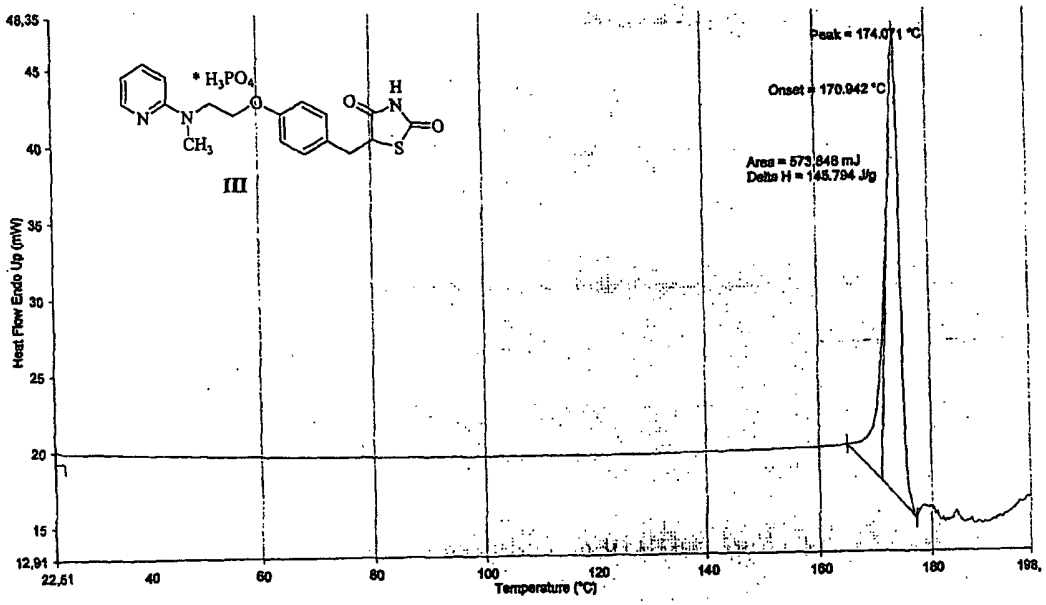


Figure 3 DSC curve of equimolar mixture of crystalline salt of phosphoric acid with rosiglitazone (III) and free base of rosiglitazone (I) prepared according to EXAMPLE 3

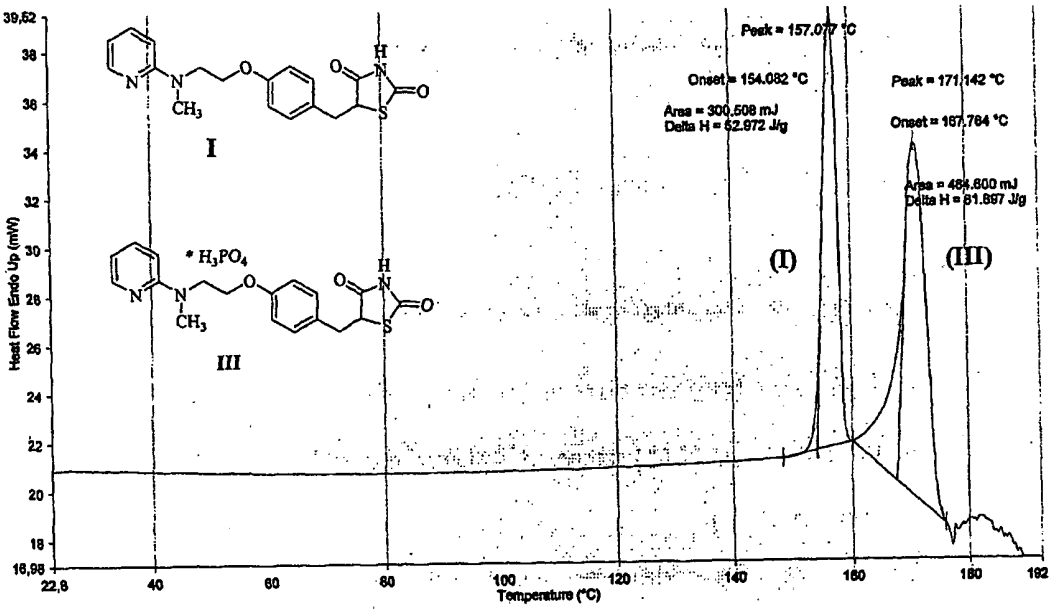


Figure 4 ^{13}C CP-MAS NMR spectrum of crystalline salt of phosphoric acid with rosiglitazone (III) prepared according to EXAMPLE 1

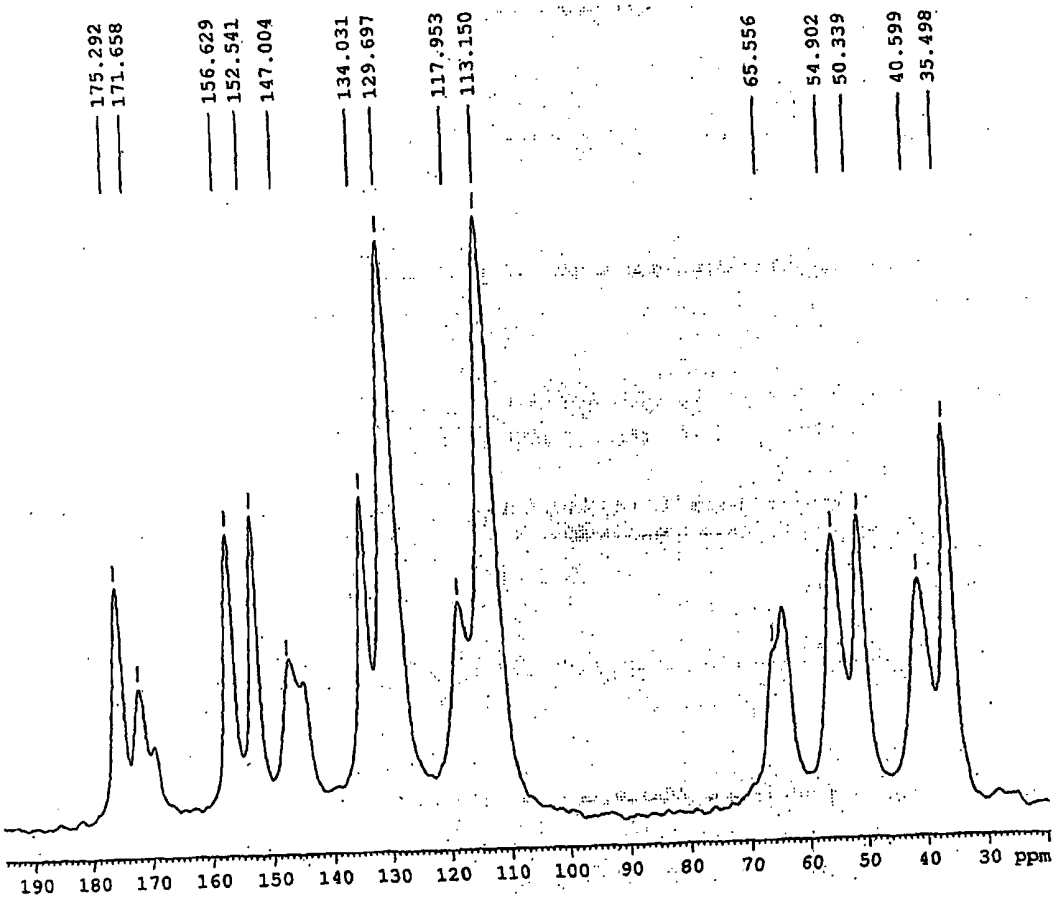


Figure 5 ^{31}**P CP-MAS NMR spectrum of crystalline salt of phosphoric acid with rosiglitazone (III) prepared according to EXAMPLE 1**

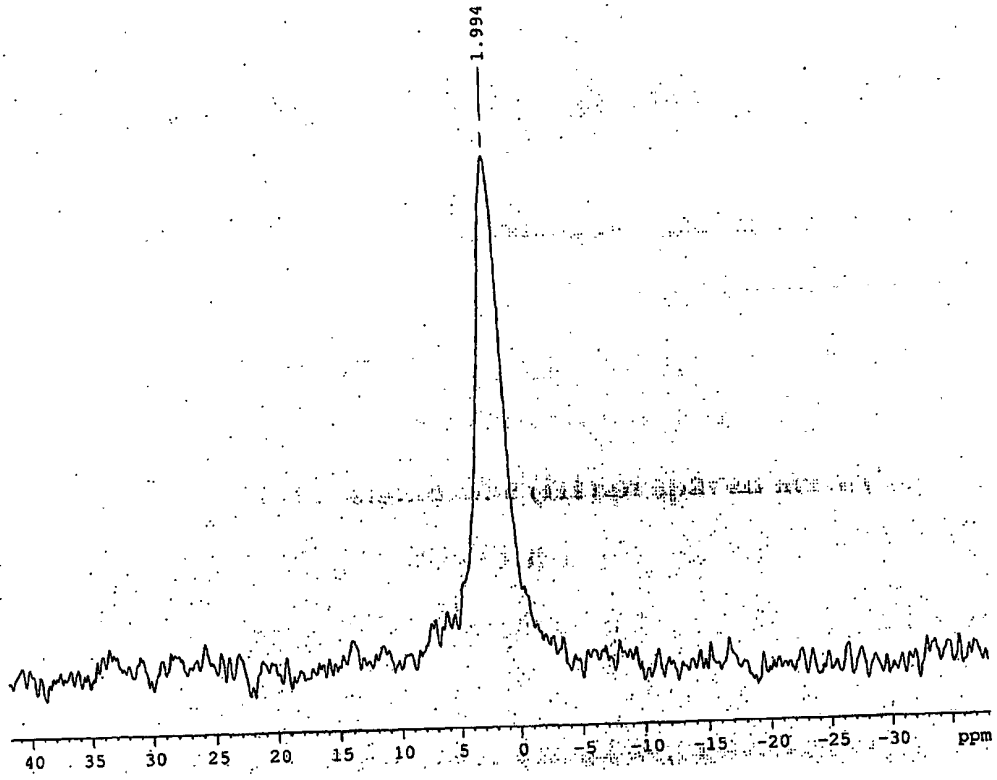


Figure 6 FT-IR spectrum of crystalline salt of phosphoric acid with rosiglitazone (III) prepared according to EXAMPLE 1

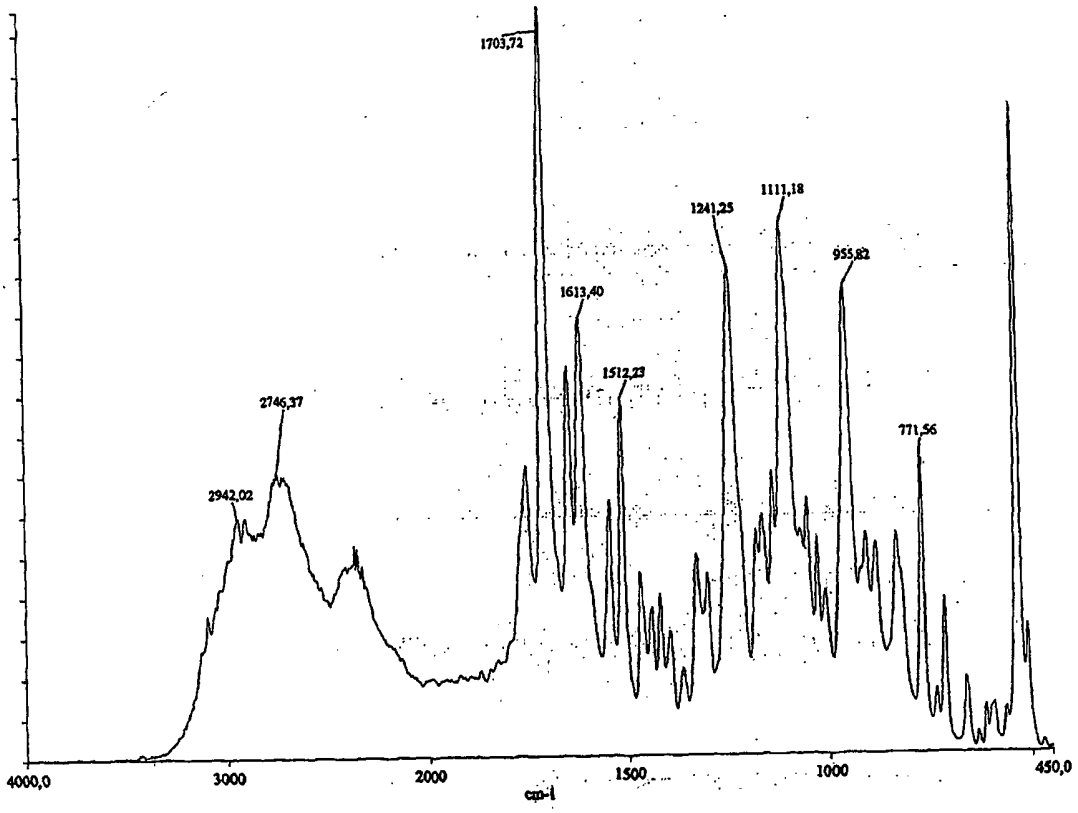
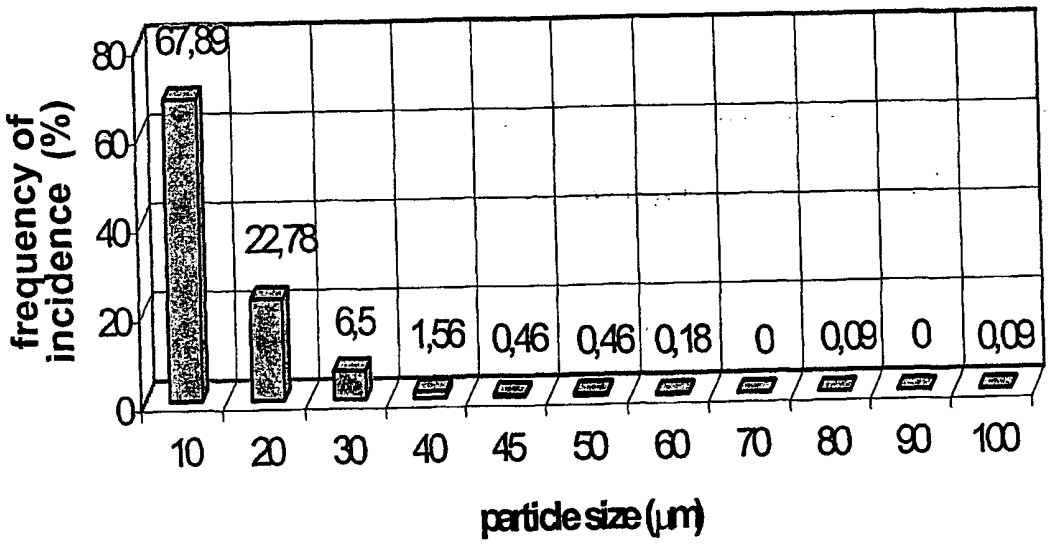


Figure 7 Diagram of distribution of particle sizes according to the maximum dimension (MaxFeret) for the crystalline salt of phosphoric acid with rosiglitazone (III) prepared according to EXAMPLE 1



INTERNATIONAL SEARCH REPORT

International Application No
PCT/CZ2005/000040

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D417/12 A61K31/4402 A61K31/4439 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
5 October 2005	17/10/2005

Name and mailing address of the ISA	Authorized officer
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